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(54) CARBAZOLES

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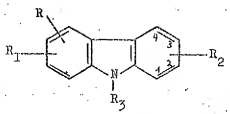
ABSTRACT

The invention relates to carbazoles of the formula



I

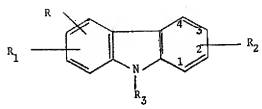
wherein R is hydrogen, halogen, hydroxy, cyano, lower alkyl, hydroxy-lower alkyl, lower alkoxy, acyl, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-lower alkoxy, nitro, amino, mono- or di-lower alkylamino, sulfamoyl, di-lower alkylsulfamoyl or difluoromethylsulfonyl; R_1 is halogen, hydroxy, cyano, lower alkyl, hydroxy-lower alkyl, lower alkoxy, acyl, acylamido, benzyloxy, lower alkylthio, trifluoromethyl, carboxy, carbo-lower alkoxy, nitro, amino, mono- or di-lower alkylamino, sulfamoyl, di-lower alkylsulfamoyl or difluoromethylsulfonyl, or R taken together with an adjacent R_1 is also lower alkylenedioxy; R_2 is $-\left(\begin{matrix}X\\ C\\ Y\end{matrix}\right)_n - A$, wherein A is cyano, hydroxy, lower alkoxy, amino-lower alkoxy, mono- or di-lower alkylamino-lower alkoxy

or a grouping $-\overset{O}{\overset{\|}{C}}-B$, wherein B is hydroxy, carboxy, lower alkoxy, amino, hydroxyamino, mono- or di-lower alkylamino, amino-lower alkoxy or mono- or di-lower alkylamino-lower alkoxy, Y and X are hydrogen or lower alkyl; n is 1 to 7; and R_3 is hydrogen, lower alkyl, acyl, halo-substituted acyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, aralkyl or haloaralkyl; or R_1 is hydrogen, when R, X and R_3 are hydrogen, Y is lower alkyl and B is hydroxy or lower alkoxy;

and salts thereof, as well as to a process for the preparation of these compounds.

These compounds have anti-inflammatory, analgesic and anti-rheumatic properties.

The invention relates to carbazoles of the formula

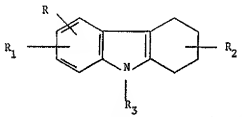


I

wherein R is hydrogen or halogen, R_1 is halogen, hydroxy, cyano, lower alkyl, lower alkoxy, acetamido, lower alkylthio, trifluoromethyl, nitro, amino, mono- or di-lower alkylamino, or di-lower alkyl sulfamoyl; R_2 is

wherein A is hydroxy, or a grouping  wherein B is hydroxy, lower alkoxy, amino, mono- or di-lower alkylamino, or di-lower alkylamino-lower alkoxy, Y and X are hydrogen or lower alkyl; n is 1 or 2; and R_3 is hydrogen, lower alkyl, lower alkanoyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl or benzyl or R_1 is hydrogen, when R, X and R_3 are hydrogen, Y is lower alkyl and B is hydroxy or lower alkoxy; the term "lower" referring to groups which contain from 1 to 4 carbon atoms, when B is hydroxy pharmaceutically acceptable salts thereof with bases; and when R_1 is amino or mono- or di-lower alkylamino, and/or when B is di-lower alkylamino-lower alkoxy, pharmaceutically acceptable addition salts thereof with acids.

The invention also relates to a process for the preparation of the compounds of the formula I and of the salts thereof as defined above, characterized in that a compound of the formula



II

wherein R, R_1, R_2 and R_3 are as above, is reacted with an aromatizing agent, that in the production of an ester of the formula I, wherein B is lower alkoxy, an obtained acid of the formula I, wherein B is hydroxy is esterified, that in the production of an acid of the formula I, wherein R_3 is carboxy-lower alkyl or B is hydroxy, an obtained ester of the formula I, wherein R_3 is lower alkoxycarbonyl-lower alkyl or B is lower alkoxy, is hydrolysed, that if desired, in an obtained compound of the formula I, wherein R_3 is a hydrogen atom, this atom is converted into a lower alkanoyl or lower alkoxycarbonyl-lower alkyl group, that in the production of a compound of the formula I, wherein R_1 is amino, an obtained compound of the formula I, wherein R_1 is acetamido, is reacted with an inorganic acid, that in the production of a compound of the formula I, wherein R_1 is di-lower alkylamino, an obtained compound of the formula I, wherein R_1 is amino, is alkylated, that in the production of a compound of the formula I, wherein R_1 or A is hydroxy, an obtained ether of the formula I, wherein R_1 or A is lower alkoxy, is hydrolysed, that, if desired, in an obtained compound of the formula I, wherein A is a hydroxy group, this group is converted into a lower alkoxy, that in the production of an alcohol of the formula I, wherein A is hydroxy, an obtained ester of the formula I, wherein B is lower alkoxy is reduced, that, if desired, in an obtained acid of the formula I, wherein B is hydroxy, or in a salt thereof with a base, the group B is converted into di-lower alkylamino-lower alkoxy, that in the production of an optically active isomer of a compound of the formula I, an obtained racemate of the formula I is

resolved into its optically active isomers and the desired isomer is isolated and that in the production of a salt of a compound of the formula I, wherein B is hydroxy or wherein R_1 is amino or mono- or di-lower alkylamino and/or B is di-lower alkylamino-lower alkoxy, such a compound of the formula I is reacted with a base or an acid.

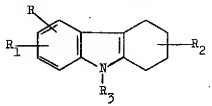
The carbazoles of formula I and the pharmaceutically acceptable salts thereof with acids and bases are useful as anti-inflammatory, analgesic and anti-rheumatic agents.

The pharmaceutically unacceptable salts of the compounds of the formula I can be converted into the compounds of the formula I or into pharmaceutically acceptable salts thereof with bases or acids by known methods.

As used herein, the term "lower alkyl" denotes a straight or branched chain hydrocarbon group containing 1-7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, neopentyl, pentyl, heptyl, and the like. The term "lower alkoxy" denotes an alkyl ether group in which the alkyl group is as described above, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy and the like. The term "lower alkylthio" denotes an alkyl thioether group in which the alkyl group is as described above, for examples, methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio and the like. The term "halogen" denotes all the halogens, that is, bromine, chlorine, fluorine and iodine; bromine and chlorine are preferred.

Exemplary of mono-lower alkylamino are methylamino, ethylamino and the like. Exemplary of di-lower alkylamino are dimethylamino, diethylamino and the like. Exemplary of amino-lower alkoxy are aminomethoxy, aminoethoxy and the like. Exemplary of mono-lower alkylamino-lower alkoxy are methylaminomethoxy, ethylaminomethoxy and the like. Exemplary of di-lower alkylamino-lower alkoxy are dimethylaminomethoxy, diethylaminoethoxy and the like. Exemplary of di-lower alkylsulfamoyl are dimethylsulfamoyl, diethylsulfamoyl and the like.

The compounds of the formula I and the salts thereof with bases or acids can be prepared by a process characterized in that a compound of the formula



II

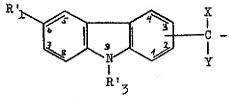
wherein R, R_1, R_2 and R_3 are as above, is reacted with an aromatizing agent, that in the production of an ester of the formula I, wherein R or R_1 is carbo-lower alkoxy or B is lower alkoxy, an obtained acid of the formula I, wherein R or R_1 is carboxy or B is hydroxy is esterified, that in the production of an acid of the formula I, wherein R or R_1 is carboxy, R_3 is carboxy-lower alkyl or B is hydroxy, an obtained ester of the formula I, wherein R or R_1 is carbo-lower alkoxy, R_3 is lower alkoxycarbonyl-lower alkyl or B is lower alkoxy, is hydrolysed, that in the production of a compound of the formula I, wherein R_1 is

amino, an obtained compound of the formula I, wherein R_1 is acylamido, is reacted with an inorganic acid, that, if desired, in an obtained compound of the formula I, wherein R_3 is a hydrogen atom, this atom is converted into an acyl or lower alkoxycarbonyl-lower alkyl group, that in the production of a compound of the formula I, wherein R or R_1 is di-lower alkylamino, an obtained compound of the formula I, wherein R or R_1 is amino, is alkylated, that in the production of a compound of the formula I, wherein R, R_1 or A is hydroxy, an obtained ether of the formula I, wherein R, R_1 or A is lower alkoxy is hydrolysed, that, if desired, in an obtained compound of the formula I, wherein A is a hydroxy group, this group is converted into a lower alkoxy, amino-lower alkoxy or mono- or di-lower alkylamino-lower alkoxy group, that in the production of an alcohol of the formula I, wherein A is hydroxy, an obtained ester of the formula I, wherein B is lower alkoxy is reduced, that, if desired is an obtained acid of the formula I, wherein B is hydroxy, or in a salt thereof with a base, the group B is converted into amino-lower alkoxy or mono- or di-lower alkylamino-lower alkoxy, that in the production of an optically active isomer of a compound of the formula I, an obtained racemate of the formula I is resolved into its optically active isomers and the desired isomer isolated and that in the production of a salt of a compound of the formula I, wherein R or R_1 is carboxy and/or B is hydroxy or carboxy or wherein R or R_1 is amino or mono- or di-lower alkylamino and/or B or A is amino-lower alkoxy or mono- or di-lower alkylamino-lower alkoxy, such a compound of the

formula I is reacted with a base or an acid.

Preferred compounds of the formula I are those wherein A is cyano, hydroxy, lower alkoxy or $-\overset{O}{\overset{\|}{C}}-B$, particularly those wherein n is 1, A or B is hydroxy, R is hydrogen and/or R_1 is halogen.

Preferred carbazoles of the invention are also those characterized by the formula



I'

wherein A' is carboxy or hydroxymethyl;

R'_1 is halogen, lower alkyl or lower alkoxy, halogen is preferred; R'_3 is hydrogen or lower alkyl, hydrogen is preferred, and X and Y are as previously described, the 2-acids are preferred,

their enantiomers when X and Y are different, and salts of the compounds of formula I' with bases.

Preferred compounds of formula I are:

racemic 6-chloro-α-methyl-carbazole-2-acetic acid;

(+) 6-chloro-α-methyl-carbazole-2-acetic acid;

(-) 6-chloro-α-methyl-carbazole-2-acetic acid;

2-(6-chloro-2-carbazolyl)propanol;

(+) 2-(6-chloro-2-carbazolyl)propanol;

(-) 2-(6-chloro-2-carbazolyl)propanol;

6-chloro-carbazole-2-acetic acid; and

6-chloro-9-methyl-carbazole-1-acetic acid.

Exemplary of compounds of this invention corresponding to formula I are:

6-chloro-carbazole-1-acetic acid;

6-chloro-carbazole-2-acetic acid ethyl ester;

6-methyl-carbazole-3-acetic acid;

6-methoxy-carbazole-4-acetic acid;

6-chloro-α-methyl-carbazole-1-acetic acid;

9-(4-chlorobenzyl)-6-methoxy-carbazole-2-acetic acid;

6-nitro-carbazole-3-acetic acid;

7-chloro-carbazole-4-acetic acid;

6-chloro-carbazole-2-acetic acid;

6-chloro-carbazole-3-acetic acid ethyl ester;

6-methyl-carbazole-4-acetic acid;

6-methoxy-carbazole-1-acetic acid;

6-chloro-α-methyl-carbazole-2-acetic acid;

9-(4-chlorobenzyl)-6-methoxy-carbazole-3-acetic acid;

6-nitro-carbazole-4-acetic acid;

7-chloro-carbazole-1-acetic acid;

6-chloro-carbazole-3-acetic acid;

6-chloro-carbazole-4-acetic acid ethyl ester;

6-methyl-carbazole-1-acetic acid;

6-methoxy-carbazole-2-acetic acid;

6-chloro-α-methyl-carbazole-3-acetic acid;
9-(4-chlorobenzyl)-6-methoxy-carbazole-4-acetic acid;
6-nitro-carbazole-1-acetic acid;
7-chloro-carbazole-2-acetic acid;
6-chloro-carbazole-4-acetic acid;
6-chloro-carbazole-1-acetic acid ethyl ester;
6-methyl-carbazole-2-acetic acid;
6-methoxy-carbazole-3-acetic acid;
6-chloro-α-methyl-carbazole-4-acetic acid;
9-(4-chlorobenzyl)-6-methoxy-carbazole-1-acetic acid;
6-nitro-carbazole-2-acetic acid;
7-chloro-carbazole-3-acetic acid;
7-methyl-carbazole-1-acetic acid;
8-chloro-carbazole-2-acetic acid;
6-fluoro-carbazole-3-acetic acid;
6-bromo-carbazole-4-acetic acid;
6,7-dichloro-carbazole-1-acetic acid;
5,6-dichloro-carbazole-2-acetic acid;
6-trifluoromethyl-carbazole-3-acetic acid;
6-chloro-7-methyl-carbazole-4-acetic acid;
6-chloro-5-methyl-carbazole-1-acetic acid;
9-methyl-carbazole-2-acetic acid;
7,8-dichloro-carbazole-3-acetic acid;
6-sulfamoylcarbazole-4-acetic acid;
6-difluoromethylsulfonyl-carbazole-1-acetic acid;
rac. 2-(6-chloro-2-carbazolyl)propanol-2-dimethylamino ethyl ether;
6-carbethoxy-carbazole-2-acetic acid;

5-chloro-6-sulfamylcarbazole-3-acetic acid;

6-chloro-9-(p-chlorobenzoyl)carbazole-4-acetic acid ethyl ester;

9-benzoyl-6-chloro-carbazole-1-acetic acid;

7-methyl-carbazole-2-acetic acid;

8-chloro-carbazole-3-acetic acid;

6-fluoro-carbazole-4-acetic acid;

6-bromo-carbazole-1-acetic acid;

6,7-dichloro-carbazole-2-acetic acid;

5,6-dichloro-carbazole-3-acetic acid;

6-trifluoromethyl-carbazole-4-acetic acid;

6-chloro-7-methyl-carbazole-1-acetic acid;

6-chloro-5-methyl-carbazole-2-acetic acid;

9-methyl-carbazole-3-acetic acid;

7,8-dichloro-carbazole-4-acetic acid;

6-sulfamoylcarbazole-1-acetic acid;

6-difluoromethylsulfonyl-carbazole-2-acetic acid;

6-carbethoxy-carbazole-3-acetic acid;

5-chloro-6-sulfamylcarbazole-4-acetic acid;

6-chloro-9-(p-chlorobenzoyl)carbazole-1-acetic acid ethyl ester;

9-benzoyl-6-chloro-carbazole-2-acetic acid;

7-methyl-carbazole-3-acetic acid;

8-chloro-carbazole-4-acetic acid;

6-fluoro-carbazole-1-acetic acid;

6-bromo-carbazole-2-acetic acid;

rac. 2-(6-chloro-2-carbazolyl)propanol methyl ether;

6,7-dichloro-carbazole-3-acetic acid;

5,6-dichloro-carbazole-4-acetic acid;

6-trifluoromethyl-carbazole-1-acetic acid;

6-chloro-7-methyl-carbazole-2-acetic acid;

6-chloro-5-methyl-carbazole-3-acetic acid;

9-methyl-carbazole-4-acetic acid;

7,8-dichloro-carbazole-1-acetic acid;

6-sulfamoylcarbazole-2-acetic acid;

6-difluoromethylsulfonyl-carbazole-3-acetic acid;

6-carbethoxy-carbazole-4-acetic acid;

5-chloro-6-sulfamylcarbazole-1-acetic acid;

6-chloro-9-(p-chlorobenzoyl)carbazole-2-acetic acid ethyl ester;

9-benzoyl-6-chloro-carbazole-3-acetic acid;

7-methyl-carbazole-4-acetic acid;

8-chloro-carbazole-1-acetic acid;

6-fluoro-carbazole-2-acetic acid;

6-bromo-carbazole-3-acetic acid;

6,7-dichloro-carbazole-4-acetic acid;

5,6-dichloro-carbazole-1-acetic acid;

6-trifluoromethyl-carbazole-2-acetic acid;

6-chloro-7-methyl-carbazole-3-acetic acid;

6-chloro-5-methyl-carbazole-4-acetic acid;

9-methyl-carbazole-1-acetic acid;

7,8-dichloro-carbazole-2-acetic acid;

6-sulfamoylcarbazole-3-acetic acid;

6-difluoromethylsulfonyl-carbazole-4-acetic acid;

6-carbethoxy-carbazole-1-acetic acid;

5-chloro-6-sulfamylcarbazole-2-acetic acid;

6-chloro-9-(p-chlorobenzoyl)carbazole-3-acetic acid ethyl ester;

9-benzoyl-6-chloro-carbazole-4-acetic acid;

6-dimethylsulfamoyl-carbazole-1-acetic acid;

6-methylthio-carbazole-2-acetic acid;

6-benzyloxy-carbazole-3-acetic acid;

6-cyano-carbazole-4-acetic acid;

6-carboxy-carbazole-1-acetic acid;

6-ethyl-carbazole-2-acetic acid;

6,7-methylenedioxy-carbazole-3-acetic acid;

6-acetyl-carbazole-4-acetic acid;

6-iodc-carbazole-1-acetic acid;

A 6-chloro-carbazole-2-acetic acid ~~dimethylamino~~ dimethylaminoethyl ester;

6,9-dimethyl-carbazole-3-acetic acid;

6-chloro-carbazole-4-acetic acid dimethylaminoethyl ester hydrochloride;

6-chloro-N,N-dimethyl-carbazole-1-acetamide;

6-methyl-carbazole-2-acetic acid ethyl ester;

6-hydroxy-carbazole-3-acetic acid;

6-dimethylsulfamoyl-carbazole-2-acetic acid;

6-methylthio-carbazole-3-acetic acid;

6-benzyloxy-carbazole-4-acetic acid;

6-cyano-carbazole-1-acetic acid;

6-carboxy-carbazole-2-acetic acid;

6-ethyl-carbazole-3-acetic acid;

6,7-methylenedioxy-carbazole-4-acetic acid;

6-acetyl-carbazole-1-acetic acid;

6-iodo-carbazole-2-acetic acid;

[A] 6-chloro-carbazole-3-acetic acid dimethylaminoethyl ~~dimethylamino~~ ester;

6,9-dimethyl-carbazole-4-acetic acid;

6-chloro-carbazole-1-acetic acid dimethylaminoethyl ester hydrochloride;

6-chloro-N,N-dimethyl-carbazole-2-acetamide;

6-methyl-carbazole-3-acetic acid ethyl ester;

6-hydroxy-carbazole-4-acetic acid;

6-dimethylsulfamoyl-carbazole-3-acetic acid;

6-methylthio-carbazole-4-acetic acid;

6-benzyloxy-carbazole-1-acetic acid;

6-cyano-carbazole-2-acetic acid;

6-carboxy-carbazole-3-acetic acid;

6-ethyl-carbazole-4-acetic acid;

6,7-methylenedioxy-carbazole-1-acetic acid;

6-acetyl-carbazole-2-acetic acid;

6-iodo-carbazole-3-acetic acid;

6-chloro-carbazole-4-acetic acid dimethylaminoethyl ~~dimethylamine~~ ester;

6,9-dimethyl-carbazole-1-acetic acid;

6-chloro-carbazole-2-acetic acid dimethylaminoethyl ester hydrochloride;

6-chloro-N,N-dimethyl-carbazole-3-acetamide;

6-methyl-carbazole-4-acetic acid ethyl ester;

6-hydroxy-carbazole-1-acetic acid;

6-dimethylsulfamoyl-carbazole-4-acetic acid;

6-methylthio-carbazole-1-acetic acid;

6-benzyloxy-carbazole-2-acetic acid;

6-cyano-carbazole-3-acetic acid;

6-carboxy-carbazole-4-acetic acid;

6-ethyl-carbazole-1-acetic acid;

6,7-methylenedioxy-carbazole-2-acetic acid;

6-acetyl-carbazole-3-acetic acid;

6-iodo-carbazole-4-acetic acid;

A 6-chloro-carbazole-1-acetic acid ~~dimethylamino~~ dimethylaminoethyl ester;

6,9-dimethyl-carbazole-2-acetic acid;

6-chloro-carbazole-3-acetic acid dimethylamino ethyl ester hydrochloride;

6-chloro-N,N-dimethyl-carbazole-4-acetamide;

6-methyl-carbazole-1-acetic acid ethyl ester;

6-hydroxy-carbazole-2-acetic acid;

7-chloro-carbazole-2-acetic acid ethyl ester;

8-chloro-carbazole-2-acetic acid ethyl ester;

6-bromo-carbazole-2-acetic acid ethyl ester;

6-methyl-carbazole-2-acetic acid ethyl ester;

7-chloro-carbazole-3-acetic acid ethyl ester;

6-chloro-9-benzyl-carbazole-2-acetic acid ethyl ester;

6-chloro-9-methyl-carbazole-2-acetic acid ethyl ester;

6-chloro-α,9-dimethyl-carbazole-2-acetic acid ethyl ester;

6-acetamidocarbazole-2-acetic acid ethyl ester;

6-methyl-9-benzyl-carbazole-1-acetic acid ethyl ester;

6-chloro-9-methyl-carbazole-1-acetic acid ethyl ester;

6-chloro-carbazole-2-propionic acid ethyl ester;

6-chloro-α,α-dimethyl-carbazole-2-acetic acid ethyl ester;

6-chloro-carbazole-1-acetic acid ethyl ester;

6-chloro-carbazole-4-acetic acid ethyl ester;

6-trifluoromethyl-carbazole-2-acetic acid ethyl ester;

7,8-dichloro-carbazole-2-acetic acid ethyl ester;

5,6-dichloro-carbazole-2-acetic acid ethyl ester;

6-methylthio-carbazole-2-acetic acid ethyl ester;

6-carbethoxy-carbazole-2-acetic acid ethyl ester;

6-fluoro-carbazole-2-acetic acid ethyl ester;

α-methyl-carbazole-2-acetic acid ethyl ester;

α-methyl-carbazole-3-acetic acid ethyl ester;

6-N,N-dimethylsulfamoyl-carbazole-2-acetic acid ethyl ester;

6-cyano-carbazole-2-acetic acid ethyl ester;

6,7-dichloro-carbazole-2-acetic acid ethyl ester;

6-nitro-carbazole-2-acetic acid ethyl ester;

and the like.

The compound of formula II is converted to the compound of formula I utilizing an aromatizing agent, for example, p-chloranil, o-chloranil, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), sulfur, palladium on carbon, lead oxide and the like, in the presence of a solvent, for example, xylene, benzene, toluene, quinoline, dimethylsulfoxide (DMSO), dimethylformamide (DMF). The aromatization is carried out at a temperature in the range of from about room temperature to about the reflux temperature of the reaction mixture; preferably, it is carried out at the reflux temperature of the reaction mixture. The compound of formula I can be separated from the reaction mixture by known procedures, included among which are, for example, filtration, cyclization and the like.

Alternatively, an acid of formula I, e.g. prepared from the corresponding acid of formula II, wherein R_2 is carboxy, can be converted to the corresponding ester by known procedures. For instance, (a) an acid of formula I can be reacted with an alkanol such as methanol, ethanol, propanol or the like, in the presence of an acid catalyst, for example, a hydrohalic acid such as hydrochloric acid, hydrobromic acid or the like, at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture, or (b) an alkali metal salt of an acid of formula I, such as the sodium salt, can be reacted with a substituted or unsubstituted alkyl halide utilizing known reaction conditions, for example, in an inert solvent such as benzene, toluene, dimethylformamide or the like, at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture.

An acid of formula I, wherein R_2 is hydrogen, can be acylated on the indole nitrogen utilizing the following reaction sequence. The acid is treated with 1,1-carbonyldiimidazole and a solvent such as tetrahydrofuran or the like, at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture. The resulting product is then treated with t-butyl alcohol in the presence of a catalytic amount of sodium-t-butoxide. Then, the resulting t-butyl ester is treated with an organic acid halide or organic anhydride, for example, an alkanoic acid halide such as acetic acid halide or an alkanoic anhydride such as acetic anhydride utilizing known reaction conditions, for example,

at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture, whereby the corresponding N-acylated ester is obtained. Pyrrolysis of this ester neat or in an inert high boiling solvent such as mineral oil or the like, at or about 160°C. until the evolution of gas ceases, gives the corresponding N-acylated acid.

A compound of formula I, wherein R_3 is lower alkoxycarbonyl-lower alkyl or acyl, can be obtained from the corresponding compound of formula I, wherein R_3 is hydrogen, utilizing known procedures, for example, by reaction with a lower alkoxycarbonyl-lower alkyl halogenide, e.g. with ethyl chloroacetate, in an inert organic solvent such as dimethylformamide, in the presence of an alkali metal carbonate such as potassium carbonate, or by reacting the alkali metal salt of the indole nitrogen prepared in the usual manner for example with sodium, sodium hydride, or sodium amide in an inert solvent, with ethyl chlorocarbonate in DMF.

A compound of formula I, wherein R or R_1 is amino, can be converted to the corresponding compound wherein R or R_1 is dialkylamino, utilizing known procedures, for example, utilizing hydrogen at a pressure of from about 1 atmosphere to about serveral atmospheres and a catalyst such as Raney nickel, together with an alkyl aldehyde such as formaldehyde, at a temperature in the range of from about room temperature

to about 100°C, in a solvent, for example, an alkanol such as methanol, ethanol, or the like.

A compound of formula I, wherein R, R_1 or A is alkoxy, can be converted to the corresponding compound, wherein R, R_1 or A is hydroxy, by known procedures. For example, a compound of formula I bearing an alkoxy group can be treated with a mineral acid, for example, a hydrohalic acid such as hydrobromic acid, or the like, in a solvent, for example, alkanols such as ethanol, propanol, or the like, at a temperature in the range of from about room temperature to about the reflux temperature of the reaction mixture. The conversion can also be effected utilizing a Lewis acid, such as aluminum tribromide, boron trifluoride, tin tetrachloride or the like, in a solvent such as benzene, toluene, dimethylformamide or the like.

An alcohol of formula I, i.e., an alcohol prepared from the corresponding alcohol of formula II, wherein A is hydroxy, can be converted to the corresponding compound of formula I wherein A is lower alkoxy, amino-lower alkoxy or mono- or di-lower alkylamino-lower alkoxy by known procedures. For example, an alcohol of formula I, wherein A is hydroxy, is treated with an alkali metal such as sodium. The resulting compound is then treated with a halide of the formula RX, wherein X is a halogen atom and R is lower alkyl, amino-lower alkyl or mono- or di-lower alkylamino-lower alkyl, utilizing known reaction conditions.

A compound of formula I, wherein R or R_1 is carbo-lower alkoxy or B is lower alkoxy, can be deesterified to the corresponding compound of formula I wherein R or R_1 is carboxy or B is hydroxy, with an alkali hydroxide, such as sodium hydroxide, potassium hydroxide or the like, in the presence of a solvent, for example, an alkanol such as methanol, ethanol or the like. The de-esterification can be carried out at a temperature in the range of from about room temperature to about the reflux temperature of the reaction mixture; preferably, it is carried out at the reflux temperature of the reaction mixture. The compound of formula I can be separated from the reaction mixture by known procedures.

An ester of formula I can be converted to the corresponding alcohol, e.g., wherein A is hydroxy, by known procedures. For example, an ester of formula I can be treated with a reagent such as lithium aluminum hydride, at a temperature in the range of from about room temperature to the reflux temperature of the reaction mixture. Thereafter, the corresponding alcohol which is formed can be separated by known procedures.

A compound of formula I, wherein R_1 is acylamido, can be converted to the corresponding compound of formula I, wherein R_1 is amino, by treatment with an inorganic acid, for example a hydrohalic acid such as hydrochloric acid or the like, utilizing known reaction conditions.

An acid of formula I, e.g. a compound of formula I, wherein B is hydroxy, or a salt of such an acid with a base,

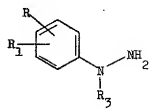
can be converted to a compound of formula I wherein B is amino-lower alkoxy or mono- or di-lower alkylamino-lower alkoxy by known procedures. For example, a salt of an acid of formula I is reacted with an amino-lower alkyl halide or a mono- or di-lower alkylamino-lower alkyl halide, exemplary of which are aminoethyl chloride, methylamino-ethyl bromide, diethylaminomethyl chloride and the like, to yield the desired end product. The temperature at which the reaction is effected is not critical; conveniently, the reaction is carried out at a temperature in the range of from about room temperature and about the reflux temperature of the reaction mixture. Conveniently, the reaction can be carried out in a polar solvent, such as dimethylformamide, dimethylsulfoxide or the like. The molar ratio of reactants is not critical. Preferably, the reactants are utilized in a 1:1 molar ratio.

The compounds of formula I, when R or R_1 is carboxy and/or B is hydroxy or carboxy, form salts with bases, e.g. pharmaceutically acceptable bases. Exemplary of such bases are alkali metal hydroxides, such as sodium hydroxide, potassium hydroxide, and the like; alkaline earth hydroxies, such as calcium hydroxide, barium hydroxide and the like; sodium alkoxides, such as sodium etholate, potassium etholate and the like; organic bases such as piperidine, diethanolamine, N-methylglucamine, and the like. Also included are the aluminum salts of the compounds of formula I, as above.

Since the compounds of the invention when X and X in formula I are different possess an asymmetric carbon atom, they are ordinarily obtained as racemic mixtures. The resolution of such racemates into the optically active isomers can be carried out by known procedures. Some racemic mixtures can be precipitated as eutectics and can thereafter be separated. Chemical resolution is, however, preferred. By this method, diastereomers are formed from the racemic mixture with an optically active resolving agent, for example, an optically active base, such as d-α-methylbenzylamine, which can be reacted with the carboxyl group. The formed diastereomers are separated by selective crystallization and converted to the corresponding optical isomer. Thus, the invention covers the racemates of the compound of formula I as well as their optically active isomers.

The compounds of the formula II utilized as starting materials in the above process can be prepared as follows:

A hydrazine of the formula

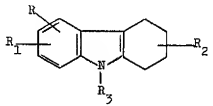


III

wherein R, R_1 and R_3 are as previously described, is reacted with a cyclohexanone of the formula

IV

wherein R_2 is as previously described,
to yield a compound of the formula



II

wherein R, R_1, R_2 and R_3 are as previously described.

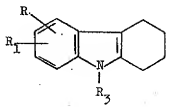
The compound of formulas III and IV are known compounds or can be prepared according to known procedures.

The reaction of the hydrazine of formula III with the cyclohexanone of formula IV to yield the corresponding 1,2,3,4-tetrahydrocarbazole of formula II is carried out at a temperature in the range of from about room temperature to about the reflux temperature of the reaction mixture; preferably, it is carried out at the reflux temperature of the reaction mixture. The reaction is effected in the presence of a solvent, for example, water, a lower alkanol, such as methanol, ethanol or the like, acetic acid, formic acid, hexane, dioxane, benzene, toluene, dimethylformamide and the like, and an acidic condensing agent as used in the Fischer Indole synthesis, for example, hydrochloric acid, sulfuric acid, phosphoric acid, zinc chloride, copper chloride, boron trifluoride and the like, and various

combinations thereof. The molar ratio of the reactants is not critical. Preferably, the reactants are utilized in a 1:1 molar ratio. Alternatively, the reaction of the hydrazine of formula III with the cyclohexanone of formula IV can be effected by thermal cyclization with or without solvent. Conveniently, such cyclization is effected at an elevated temperature, for example, at a temperature in the range of from about 80°C to about 200°C. The compound of formula II can be separated from the reaction mixture by known procedures. If desired, however, the reaction mixture may be utilized in the next step, i.e. the aromatisation to a compound of formula I, without further separation.

The compounds of formula II, wherein R_2 is $-CH_2COOH$ at the 1-position can also be prepared as illustrated hereinbelow.

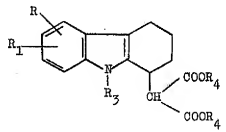
A compound of the formula



V

wherein R, R_1 and R_3 are as previously described, is treated with freshly prepared N-halo-succinimide and pyridine in the presence of an inert organic solvent, for example, a hydrocarbon such as benzene or the like, and this reaction mixture is treated with a dialkylmalonate in the

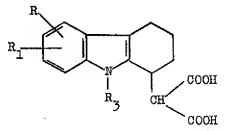
presence of an alkaline carbonate such as potassium carbonate, to yield a compound of the formula



VI

wherein R, R_1 and R_3 are as previously described and R_4 is lower alkyl.

The compound of formula VI is then treated with an alkali metal hydroxide such as potassium hydroxide in the presence of alkanol such as ethanol or the like, at the reflux temperature of the reaction mixture to yield the malonic acid of the formula

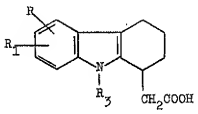


VII

wherein R, R_1 and R_3 are as previously described.

Subsequently, the malonic acid of formula VII is heated neat or in the presence of an inert high boiling solvent such as mineral oil or the like, under an atmosphere of dry

nitrogen to yield the acid of the formula



VIII

wherein R, R_1 and R_3 are as previously described.

Exemplary of the compounds of formula II, which can be utilized as starting materials in the process of the invention are:

6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

6-methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid;

6-methoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-methoxy-1,2,3,4-tetrahydrocarbazole-4-acetic acid;

6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester;

9-(4-chlorobenzyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-nitro-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

7-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

7-chloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid;

7-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

8-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid methyl ester;

8-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-fluoro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-bromo-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6,7-dichloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid;

5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-methyl-α-methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

6-chloro-7-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-chloro-5-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

9-methyl-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

7,8-dichloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid;

1,2,3,4-tetrahydro-6-sulfamoylcarbazole-4-acetic acid;

6-difluoromethylsulfonyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

6-carbethoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

5-chloro-1,2,3,4-tetrahydro-6-sulfamylcarbazole-2-acetic acid;

6-carbethoxy-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

6-chloro-9-(p-chlorobenzoyl)-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

9-benzoyl-6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-dimethylsulfamoyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-methylthio-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-benzyloxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-cyano-1,2,3,4-tetrahydrocarbazole-4-acetic acid;

6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-ethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6,7-methylenedioxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-acetyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

6-iodo-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid dimethylaminoethyl ester;

6,9-dimethyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid;

6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid dimethylaminoethyl ester hydrochloride;

6-chloro-N,N-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetamide;

6-methyl-α-methyl-1,2,3,4-tetrahydrocarbazole-4-acetic acid ethyl ester;

6-hydroxy-1,2,3,4-tetrahydrocarbazooe-2-acetic acid;

and the like.

Exemplary of the compounds of formula III, which can be utilized in the above process are:

p-chlorophenylhydrazine;
m-chlorophenylhydrazine;
o-chlorophenylhydrazine;
p-fluorophenylhydrazine;
p-bromophenylhydrazine;
3,4-dichlorophenylhydrazine;
p-trifluoromethylphenylhydrazine;
4-chloro-1-methylphenylhydrazine;
2,3-dichlorophenylhydrazine;
p-methylphenylhydrazine;
m-methylphenylhydrazine;
p-methoxyphenylhydrazine;
N^1-(4-chlorobenzyl)-p-chlorophenylhydrazine;
p-nitrophenylhydrazine;
1-methyl-1-phenylhydrazine;
p-sulfamidophenylhydrazine;
p-(difluoromethylsulfonyl)-phenylhydrazine;
p-carbethoxyphenylhydrazine;
4-aminosulfonyl-3-chlorophenylhydrazine; and the like.

The compounds of formula III are known compounds or can be prepared in an analogous manner to the known compounds.

Exemplary of the compounds of formula IV, which can be utilized in the above process are:

α-methyl-1-oxo-cyclohexane-acetic acid;

α-methyl-2-oxo-cyclohexane-acetic acid;

α-methyl-3-oxo-cyclohexane-acetic acid;

α-methyl-4-oxo-cyclohexane-acetic acid;

1-oxo-cyclohexane-acetic acid;

2-oxo-cyclohexane-acetic acid;

3-oxo-cyclohexane-acetic acid;

4-oxo-cyclohexane-acetic acid;

α-methyl-1-oxo-cyclohexane-acetic acid ethyl ester;

α-methyl-1-oxo-cyclohexane-acetic acid methyl ester;

1-oxo-cyclohexane-acetic acid ethyl ester;

1-oxo-cyclohexane-acetic acid methyl ester; and the like.

The compounds of formula IV are known compounds or can be prepared in an analogous manner to the known compounds.

The compounds of formula I, including the salts of those compounds of formula I which form salts with pharmaceutically acceptable bases and acids, possess anti-inflammatory, analgesic and anti-rheumatic activity, and are therefore useful as anti-inflammatory, analgesic and anti-rheumatic agents. The compounds of formula I also exhibit a significantly low incidence of ulcerogenic activity, which renders them highly desirable as anti-inflammatory, analgesic and anti-rheumatic agents. Their pharmacologically useful activities are demonstrated in warm-blooded animals using standard procedures.

For example, the anti-inflammatory activity is demonstrated in Albino rats of Hart Strain, weighing 125-155 g. The test animals are given 10 ml of vehicle[1], which contains the test compound per kg of body weight. The animals are treated daily for 5 consecutive days. Three hours after the first treatment, 0.05 ml of an 0.5 percent suspension of heat killed dessiccated Mycobacterium butyricum in olive oil, which has been steam sterilized for 30 minutes, is injected into the right hind foot of each rat. The paw volume is measured immediately after the injection of the adjuvant and again 96 hours later. The difference is recorded as volume of edema. The paw volume is measured by immersion of the paw into a column of mercury to an ink mark exactly at the level of the lateral malleolus. Percent inhibition is calculated by dividing the average control edema minus the average treatment edema by the average control edema times 100. The percent inhibition is plotted against dose on semi-logarithmic probability paper and the dose required to produce a 30 percent reduction in edema is estimated therefrom and is expressed as ED_{30}.

When 6-chloro-α-methyl-carbazole-2-acetic acid, which has demonstrated an LD_{50} of, for example, 400 mg p.o. in mice, is utilized as the test substance at a dosage of 0.03 mg p.o., an anti-inflammatory activity is observed (ED_{30} = 0.17).

[1] Hilgar, A.G. and Hummel, D. J.: Endocrine Bioassay Data, No. 1, p. 15, August 1964 (Cancer Chemotherapy National Service Center, N.I.H.)

The analgesic activity of the compounds of the invention is demonstrated, for example, employing the method which is a modification of that described by Eddy (1950), Wolfe and MacDonald (1944) and Eddy and Leimbach (1952). The method determines the reaction time of mice dropped onto a hot plate maintained at 55 ± 0.5°C. Six groups of male mice (5 mice/group) weighing between 20-30 grams are utilized. The initial reaction time of these mice is determined once, and the reaction time of each group is then averaged. The mice are then administered the vehicle and/or the compound to be tested by the oral, intraperitoneal or subcutaneous route. The average reaction time of each group is determined again at 30, 60 and 90 minutes after compound administration and is compared to controls. Reaction time is recorded as percent changes from control. All groups are averaged before and after treatment. A combined reaction time average (recorded as percent change of reaction time threshhold from controls) for all three periods is plotted against dose on graph paper, and a curve is drawn. The ED_{50} is read from this curve.

When 6-chloro-α-methyl-carbazole-2-acetic acid, which has demonstrated an LD_{50} of, for example, 400 mg p.o. in mice, is utilized as the test substance analgesic activity is observed at an ED_{50} of 15.

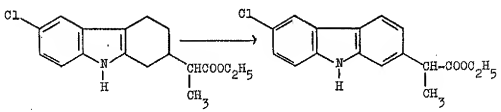
The compounds of formula I, their enantiomers and salts thereof as herein described, have effects qualitatively similar to those of phenylbutazone and indomethacin, known for their

therapeutic uses and properties. Thus, the end products of this invention demonstrate a pattern of activity associated with anti-inflammatory agents of known efficacy and safety.

The compounds of formula I, their enantiomers and salts thereof as herein described, can be incorporated into standard pharmaceutical dosage forms, for example, they are useful for oral or parenteral application with the usual pharmaceutical adjuvant material, for example, organic or inorganic inert carrier materials such as water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene-glycols, and the like. The pharmaceutical preparations can be employed in a solid form, for example, as tablets, troches, suppositories, capsules, or in liquid form, for example, as solutions, suspensions or emulsions. Pharmaceutical adjuvant materials can be added and include preservatives, stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

Example 1

Preparation of 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester



(d) (e)

A mixture of 34.9 g of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (mixture of diastereomers), 350 ml xylene and 56.0 g of p-chloranil is stirred and heated under an atmosphere of dry nitrogen. The reaction flask is wrapped in aluminum foil in order to keep out any extraneous light. After the reaction mixture is stirred at reflux temperature for 6 hours, heating and stirring are stopped and the reaction mixture is left overnight at room temperature. The supernatant liquid is decanted through a filter. The residue is triturated with 100 ml of warm benzene and the supernatant liquid is decanted through a filter. This process is repeated 3 more times. Ether (300 ml) is added to the combined filtrates. The solution is extracted with cold 2N sodium hydroxide (3 x 100 ml), washed by extraction with water until neutral and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the solvent, a residue of 35.5 g remains. Crystallization from 50 ml of methanol gives 14.8 g

of 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester, m.p. 106-107.5°C (43.2%).

In an analogous manner, when the 1,2,3,4-tetrahydrocarbazole of formula (d) is replaced as hereinafter set forth, the corresponding carbazoles are obtained:

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-chlorocarbazole-2-acetic acid ethyl ester, m.p. 176-178°C (methanol);

substituting 7-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 7-chlorocarbazole-2-acetic acid ethyl ester, m.p. 200-202°C (methanol); and

substituting 8-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 8-chlorocarbazole-2-acetic acid ethyl ester, m.p. 110-113°C (methanol);

substituting 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-acetamidocarbazole-2-acetic acid ethyl ester, m.p. 208-210°C (ethanol);

substituting 6-methyl-9-benzyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester for (d), there is obtained 6-methyl-9-benzylcarbazole-1-acetic acid ethyl ester, m.p. 130-131°C (CH_3OH);

substituting 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester for (d), there is obtained 6-chloro-9-ethylcarbazole-1-acetic acid ethyl ester;

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid ethyl ester for (d) there is obtained 6-chlorocarbazole-2-propionic acid ethyl ester, m.p. 149-150.5°C (methanol);

substituting 6-chloro-α.α-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-chloro-α,α-dimethylcarbazole-2-acetic acid ethyl ester;

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester for (d), there is obtained 6-chlorocarbazole-1-acetic acid ethyl ester, m.p. 152.5-154°C (CH_3OH);

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid ethyl ester for (d), there is obtained 6-chlorocarbazole-4-acetic acid ethyl ester, m.p. 154-155°C (methanol);

substituting 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-trifluoromethylcarbazole-2-acetic acid ethyl ester, m.p. 130-131°C (CCl_4);

substituting 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 7,8-dichlorocarbazole-2-acetic acid ethyl ester, m.p. 154-155°C (methanol);

substituting 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 5,6-dichlorocarbazole-2-acetic acid ethyl ester, m.p. 139-140°C (methanol);

substituting 6-methylthio-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-methylthiocarbazole-2-acetic acid ethyl ester;

substituting 6-carbethoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-carbethoxycarbazole-2-acetic acid ethyl ester, m.p. 141-143°C (methanol);

substituting 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-fluorocarbazole-2-acetic acid ethyl ester, m.p. 178-179°C (methanol);

substituting α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained α-methylcarbazole-2-acetic acid ethyl ester, m.p. 104-105°C (hexane);

substituting α-methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid ethyl ester for (d), there is obtained α-methylcarbazole-3-acetic acid ethyl ester, m.p. 97.5-99°C (CH_3OH);

substituting 6-N,N-dimethylsulfamoyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-N,N-dimethylsulfamoylcarbazole-2-acetic acid ethyl ester, m.p. 146-147°C (CH_3OH);

substituting 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-cyanocarbazole-2-acetic acid ethyl ester, m.p. 157-158°C (CH_3OH);

substituting 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6,7-dichlorocarbazole-2-acetic acid ethyl ester, m.p. 186-187.5°C (CH_3OH); and

substituting 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester for (d), there is obtained 6-nitrocarbazole-2-acetic acid ethyl ester, m.p. 164-165°C (CH_3OH).

The ester of formula d) utilized in the above process can be obtained as follows:

A. Preparation of α-methyl-3-oxocyclohexanemalonic acid diethyl ester

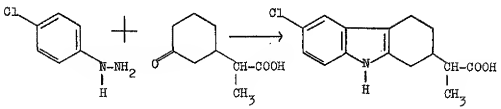
2.2 g of sodium are dissolved in 300 ml of ethanol in a 1 liter 3 neck round bottom flask equipped with a N_2 gas inlet, thermometer and dropping funnel. Diethylmethylmalonate (182 g) is added with stirring and the stirring continued for an hour. After this time, 92 g of 2-cyclohexene-1-one in 118 ml of ethanol are added slowly over the course of one hour. The stirring is continued for an additional 5 hours. The solution is then acidified with conc. acetic acid and the excess ethanol is removed on a rotating evaporator under reduced pressure. The residue is dissolved in ether (1200 ml) and washed with water (3 x 200 ml). The ether solution is dried over anhydrous Na_2SO_4 with stirring. After removal of the Na_2SO_4, the ether is removed and a residue of 308.7 g of oil is obtained. This residue is distilled to yield 204.4 g (78.7%) of α-methyl-3-oxocyclohexanemalonic acid diethyl ester as a clear oil, b.p. 149-152°C. (0.8 mm), $n_D^{20} = 1.4660$.

B. Preparation of α-methyl-3-oxocyclohexaneacetic acid

15.75 g of α-methyl-3-oxocyclohexanemalonic acid diethyl ester, 235 ml of 6N HCl and 235 ml of dioxane are combined in a 1 liter flask equipped with a reflux condensor. The solution is heated to reflux with stirring and refluxed for 10 hours. After the solution has reached room temperature, a 50% solution of NaOH (75 g NaOH-75 ml H_2O) is added until the solution is basic. The basic solution is then cooled with stirring in an ice bath before extracting it with ether (1 x 500 ml). The ether layer is discarded and the aqueous layer is made acidic with concentrated HCl. The acidic solution is concentrated to dryness on a rotating evaporator and the salt remaining is triturated with ether (3 x 350 ml). The ether solution is dried over anhydrous Na_2SO_4 with stirring.

The drying agent is removed by filtration and the ether is concentrated to dryness on a rotating evaporator to yield 13.6 g of an oily residue. The residual oil is distilled to yield 5.4 g (54.9%) of α-methyl-3-oxocyclohexaneacetic acid, b.p. 164-166°C (0.7 mm), n_D^{20} = 1.4794.

C. Preparation of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid (diastereomers)



(a) (b) (c)

A mixture of 25 g of p-chlorophenylhydrazine hydrochloride, 150 ml of 80% acetic acid (120 ml of glacial acetic plus 30 ml of water) and 23.8 g of α-methyl-3-oxocyclohexane acetic acid is stirred at ambient temperature under an atmosphere of nitrogen. After 1.5 hours, solution is complete and the reaction is heated to reflux. After 10 minutes at reflux, a heavy precipitate forms. Following an additional 0.5 hour under reflux, the heat is removed and the reaction mixture is stirred while cooling to room temperature. The contents of the reaction flask are poured into 2 liters of stirred water. The mixture is stirred for an additional 20 minutes and filtered. The filter cake is washed with water, allowed to dry and then completely dried in a vacuum oven (95°C, over sodium hydroxide, water pump pressure); yield, 36.3 g (93%) of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 193-202°C (mixture of diastereomers).

In an analogous manner, when the phenylhydrazine of formula (a) and/or the oxocyclohexane of formula (b) are

replaced, as hereinafter set forth, the corresponding 1,2,3,4-tetrahydrocarbazoles are obtained:

substituting cyclohexane-3-acetic acid for (b) there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 184-186°C (benzene);

substituting m-chlorophenylhydrazine for (a) and cyclohexane-3-acetic acid for (b) there is obtained 7-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 189-192°C (ethyl acetate);

substituting o-chlorophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b) there is obtained 9-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

substituting p-bromophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b) there is obtained 6-bromo-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 191-201°C (ethyl acetate);

substituting p-methylphenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b) there is obtained 6-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 184-186°C (ethyl acetate);

substituting p-methoxyphenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b) there is obtained 6-methoxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 187-188°C (ethyl acetate);

substituting cyclohexanone-4-acetic acid for (b) there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid, m.p. 186-188°C (ethyl acetate);

substituting m-chlorophenylhydrazine for (a) and cyclohexanone-4-carboxylic acid for (b) there is obtained 7-chloro-1,2,3,4-tetrahydrocarbazole-3-acetic acid, m.p. 186-188°C (hexane/ethyl acetate);

substituting 1-methyl-1-p-chlorophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b) there is obtained 6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 202-204°C (ethyl acetate);

substituting 1-methyl-1-p-chlorophenylhydrazine for (a) there was obtained 6-chloro-α,9-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid (diastereomers), m.p. 197-203°C (ethyl acetate);

substituting 1-benzyl-1-p-methylphenylhydrazine for (a) and cyclohexanone-1-acetic acid ethyl ester for (b) there is obtained 6-methyl-9-benzyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester;

substituting 1-methyl-1-p-chlorophenylhydrazine for (a) and cyclohexanone-1-acetic acid ethyl ester for (b) there is obtained 6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester;

substituting p-dimethylsulfamoylphenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 1,2,3,4-tetrahydro-6-dimethylsulfamoylcarbazole-2-acetic acid, m.p. 159-161°C (ethyl acetate);

substituting p-cyanophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

substituting 3,4-dichlorophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 192-193°C (ethyl acetate);

substituting p-nitrophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 233-234°C (methanol);

substituting phenylhydrazine for (a) there is obtained α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

substituting phenylhydrazine for (a) and α-methyl-4-oxocyclohexane acetic acid for (b), there is obtained α-methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid;

substituting cyclohexanone-3-acetic acid for (b) there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid, m.p. 162.5-163.5°C (benzene);

substituting p-trifluoromethylphenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 186-187°C (ethanol/H_2O);

substituting 2,3-dichlorophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 167-169°C (benzene);

substituting 3,4-dichlorophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 194-196°C (acetonitrile);

substituting p-methylthiophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 1,2,3,4-tetrahydro-6-methylthiocarbazole-2-acetic acid, m.p. 204-205°C (ethyl acetate);

substituting p-carboxyphenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 306-307°C (ethanol);

substituting p-fluorophenylhydrazine for (a) and cyclohexanone-2-acetic acid for (b), there is obtained 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 189-190°C (ethyl acetate);

substituting α,α-dimethyl-3-oxocyclohexane acetic acid for (b), there is obtained 6-chloro-α,α-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid, m.p. 242-243°C (ethyl acetate);

substituting p-acetamidophenylhydrazine for (a) and cyclohexanone-3-acetic acid for (b), there is obtained 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid;

substituting 1-ethyl-1-parachlorophenylhydrazine for (a) and cyclohexanone-2-acetic acid for (b), there is obtained 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid;

substituting cyclohexanone-3-propionic acid for (b), there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid, m.p. 211-212°C (ethyl acetate);

substituting cyclohexanone-2-acetic acid for (b) there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid, m.p. 141-142.5°C.

D. Alternative method for the preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid

a) Preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid diethyl ester

To a stirred solution of 18.8 g of 6-chloro-1,2,3,4-tetrahydrocarbazole, 20 g of pyridine and 320 ml of dry benzene are added over the course of 30 minutes 18.8 g of freshly recrystallized N-bromosuccinimide. After the addition, the reaction mixture is stirred for 2.5 hours at room temperature and then stirred for 45 minutes at 60°C. After cooling to room temperature, the reaction mixture is concentrated to dryness under reduced pressure. To the stirred residue is added a solution of 42.5 g of diethylmalonate in 265 ml of anhydrous ethanol. The stirred mixture is cooled in an ice bath to 5°C and 21.5 g of anhydrous potassium carbonate are added slowly over 30 minutes. The reaction mixture is stirred an additional 16 hours at room temperature and glacial acetic acid is added slowly until the reaction mixture is slightly acidic. The mixture is then concentrated to dryness under reduced pressure and the residue is

partitioned between ether and water. The organic layer are separated, washed by extraction with water four times and dried over anhydrous sodium sulfate. After the desiccant has been removed by filtration and the ether evaporated, the residue slowly crystallizes. The supernatant liquor is decanted and the remaining crystals are dried on a porous plate to yield 8 g of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid diethyl ester, having a m.p. of 142-144°C.

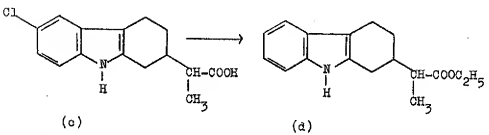
b) Preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid

A solution of 5 g of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid diethyl ester, 8 g of potassium hydroxide, 38 ml of ethanol and 2 ml of water is stirred and heated to reflux temperature under an atmosphere of nitrogen. After 2 hours of refluxing, the reaction mixture is concentrated to dryness under reduced pressure. The residue is dissolved in 1.5 liters of warm water and filtered through a celite filter pad. Concentrated hydrochloric acid is added to the cooled filtrate until precipitation is complete, and the mixture is extracted with ether. In turn, the ether extract is washed by extraction with water and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the ether solution, 4.7 g are obtained. A small portion is recrystallized from benzene to yield 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid, having a m.p. of 159-160°C (dec.).

c) Preparation of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid

Stirred anhydrous 6-chloro-1,2,3,4-tetrahydrocarbazole-1-malonic acid (4.3 g) is heated under an atmosphere of dry nitrogen. The temperature is raised to 195°C over 20 minutes and then held at 195°C for 1/2 hour to complete the decarboxylation. Carbon dioxide startes to evolve when the temperature reaches 160°C. After cooling, the reaction mixture is crystallized from benzene to yield 1.8 g of 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid, having a m.p. 141-142.5°C.

B. Preparation of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester (diastereomers)



36 g of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid (diastereomers) are dissolved in 1500 ml of ethanol. The slightly turbid solution is filtered and 10 g of hydrogen chloride (gas) are added to the clear filtrate. The solution is refluxed under an atmosphere of nitrogen for 12 hours and allowed to remain at room temperature for 48 hours. Benzene (100 ml) is added and the reaction mixture is concentrated under reduced pressure to dryness. The

residue is dissolved in 1 liter of ethanol, 11 g of hydrogen chloride (gas) are added and the solution is again refluxed. Following 12 hours at reflux, heating is stopped and 200 ml of benzene are added. Thereafter, the reaction mixture is concentrated to dryness. The residue is dissolved in 800 ml of ether (a faint turbidity remains) and extracted with 200 ml of cold 2N sodium hydroxide. After the ether solution has been washed by extraction with water, it is dried over powdered anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the ether, a gummy solid remains. Yield 35.9 g (91.2 percent theory) of 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester.

In analogous manner, when the 1,2,3,4-tetrahydrocarbazole of formula (c) is replaced as hereinafter set forth, the corresponding carbazoles are obtained:

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester, m.p. 125-126°C (ethanol);

substituting 1,2,3,4-tetrahydro-6-dimethylsulfamoylcarbazole-2-acetic acid for (c), there is obtained 1,2,3,4-tetrahydro-6-dimethylsulfamoylcarbazole-2-acetic acid ethyl ester;

substituting 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-cyano-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester, 159-160°C (benzene);

substituting 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6,7-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-nitro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting 1,2,3,4-tetrahydro-6-methylthiocarbazole-2-acetic acid for (c), there is obtained 1,2,3,4-tetrahydro-6-methylthiocarbazole-2-acetic acid ethyl ester;

substituting 6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-carboxy-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-fluoro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting 6-chloro-α,α-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-chloro-α,α-dimethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester, 169-171°C (ethyl acetate);

substituting α-methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid for (c) there is obtained α-methyl-1,2,3,4-tetrahydrocarbazole-3-acetic acid ethyl ester;

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid for (c), there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-4-acetic acid ethyl ester;

substituting 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 6-trifluoromethyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 7,8-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

substituting 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid for (c), there is obtained 5,6-dichloro-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester;

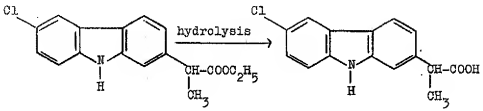
substituting 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid for (c), there is obtained 6-chloro-9-ethyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester;

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid for (c), there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-2-propionic acid ethyl ester;

substituting 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid for (c), there is obtained 6-chloro-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester.

Example 2

Preparation of 6-chloro-α-methylcarbazole-2-acetic acid (racemic)



(e) (f)

A stirred mixture of 11 g of 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester, 100 ml ethanol and 100 ml of 3N sodium hydroxide is heated (N_2 atmosphere). After 2 hours at reflux, the reaction mixture is concentrated to dryness under reduced pressure. Water (300 ml) and ice (200 g) are added to the residue and concentrated hydrochloric acid is added until the mixture is strongly acid. The acidic mixture is extracted with ether (3 x 200 ml). The ether extracts are combined, washed by extraction with water (3 x 100 ml) and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the solvent, a yield of 9.8 g (98.2%) is obtained. Crystallization from $CHCl_3$ yields 6.2 g (62.0%) of 6-chloro-α-methylcarbazole-2-acetic acid, m.p. 197-198°C. A second crop of 1.6 g, m.p. 195-199°C is obtained from the mother liquors.

In an analogous manner, when the carbazole of formula (e) is replaced as hereinafter set forth, the corresponding carbazoles of formula (f) are obtained:

substituting 6-chloro-carbazole-2-acetic acid ethyl ester for (e), there is obtained 6-chloro-carbazole-2-acetic acid, m.p. 255-257°C (ethyl acetate);

substituting 7-chloro-carbazole-2-acetic acid ethyl ester for (e), there is obtained 7-chloro-carbazole-2-acetic acid, m.p. 252-254°C (methanol);

substituting 8-chloro-carbazole-2-acetic acid ethyl ester for (e), there is obtained 8-chloro-carbazole-2-acetic acid, m.p. 210-211°C (chloroform);

substituting 6-bromo-carbazole-2-acetic acid ethyl ester for (e), there is obtained 6-bromo-carbazole-2-acetic acid, m.p. 249-250°C (methanol);

substituting 6-methyl-carbazole-2-acetic acid ethyl ester for (e), there is obtained 6-methyl-carbazole-2-acetic acid, m.p. 272-274°C (decomp.) (ethyl acetate);

substituting 6-methoxy-carbazole-2-acetic acid ethyl ester for (e), there is obtained 6-methoxy-carbazole-2-acetic acid, m.p. 205-206°C (decomp.) (ethyl acetate);

substituting 6-methyl-9-benzyl-carbazole-1-acetic acid ethyl ester for (e), there is obtained 6-methyl-9-benzyl-carbazole-1-acetic acid, m.p. 182-185°C (CH_3OH);

substituting 6-chloro-9-methyl-carbazole-1-acetic acid ethyl ester for (e), there is obtained 6-chloro-9-methyl-carbazole-1-acetic acid, m.p. 223-225°C (ethyl acetate);

substituting 6-chloro-9-methyl-carbazole-2-acetic acid ethyl ester for (e), there is obtained 6-chloro-9-methyl-carbazole-2-acetic acid, m.p. 235-236°C (ethyl acetate);

substituting rac. 6-chloro-α,9-dimethyl-carbazole-2-acetic acid ethyl ester for (e), there is obtained rac. 6-chloro-α,9-dimethyl-carbazole-2-acetic acid, m.p. 176-178°C (benzene);

substituting 6-chloro-carbazole-3-acetic acid ethyl ester for (e), there is obtained 6-chloro-carbazole-3-acetic acid, m.p. 246-247°C (ethyl acetate);

substituting 7-chloro-carbazole-3-acetic acid ethyl ester for (e), there is obtained 7-chloro-carbazole-3-acetic acid, m.p. 236-237°C (ethyl acetate);

substituting 6-acetamidocarbazole-2-acetic acid ethyl ester for (e), there is obtained 6-acetamidocarbazole-2-acetic acid, m.p. 300°C (ethanol);

substituting 6-methyl-9-benzylcarbazole-1-acetic acid ethyl ester for (e), there is obtained 6-methyl-9-benzyl-carbazole-1-acetic acid, m.p. 182-185°C (CH_3OH);

substituting 6-chloro-9-ethylcarbazole-1-acetic acid ethyl ester for (e), there is obtained 6-chloro-9-ethyl-carbazole-1-acetic acid, m.p. 192-193°C (methanol);

substituting 6-chlorocarbazole-2-propionic acid ethyl ester for (e), there is obtained 6-chlorocarbazole-2-propionic acid, m.p. 230-231°C (methanol);

substituting 6-chloro-α,α-dimethylcarbazole-2-acetic acid ethyl ester for (e), there is obtained 6-chloro-α,α-dimethylcarbazole-2-acetic acid, m.p. 221-222.5°C (ethyl acetate/hexane);

substituting 6-chlorocarbazole-1-acetic acid ethyl ester for (e), there is obtained 6-chlorocarbazole-1-acetic acid, m.p. 155-157°C (decomp.). Piperidine salt, m.p. 118-120°C (acetone/ether);

substituting 6-chlorocarbazole-4-acetic acid ethyl ester for (e), there is obtained 6-chlorocarbazole-4-acetic acid, m.p. 175-176°C (decomp.) (benzene);

substituting 6-methylthiocarbazole-2-acetic acid ethyl ester for (e), there is obtained 6-methylthiocarbazole-2-acetic acid, m.p. 202-204°C (ethyl acetate);

substituting 6-carboxycarbazole-2-acetic acid ethyl ester for (e), there is obtained 6-carboxycarbazole-2-acetic acid, m.p. 301-302°C (acetone);

substituting 6-chloro-9-carboxymethyl-α-methylcarbazole-2-acetic acid ethyl ester for (e), there is obtained 6-chloro-9-carboxymethyl-α-methylcarbazole-2-acetic acid, m.p. 248-250°C (decomp.) (acetone);

substituting α-methylcarbazole-2-acetic acid ethyl ester for (e), there is obtained α-methylcarbazole-2-acetic acid, m.p. 246-247°C (decomp.) ($CHCl_3$);

substituting α-methylcarbazole-3-acetic acid ethyl ester for (e), there is obtained α-methylcarbazole-3-acetic acid, m.p. 213-216°C (decomp.) (ethyl acetate);

substituting 6-nitrocarbazole-2-acetic acid ethyl ester for (e), there is obtained 6-nitrocarbazole-2-acetic acid, m.p. 262-264°C (CH_3OH); and

substituting 6-chloro-9-ethoxycarbonyl-α-methylcarbazole-2-acetic acid ethyl ester for (e), there is obtained 6-chloro-9-carboxymethyl-α-methylcarbazole-2-acetic acid, m.p. 248-250°C (acetone).

Example 3

Preparation of (-) 6-chloro-α-methyl-carbazole-2-acetic acid

A solution of 8.0 g of (+)-α-methylbenzylamine ($[\alpha]_D^{20}$ + 39°) in 40 ml acetone is carefully added to a warmed solution of 18.0 g of rac. 6-chloro-α-methyl-carbazole-2-acetic acid in 360 ml of acetone. After standing at room temperature for 3 days, the mixture is filtered and the filter cake is washed with a small amount of cold acetone to yield upon drying 10.6 g of (-) 6-chloro-α-methyl-carbazole-2-acetic acid (+) α-methylbenzylamine salt, $[\alpha]_D^{22}$ + 9.9° (the filtrate and washings are combined, concentrated to dryness and the free acid is liberated for use in further resolution).

A recrystallization of the salt from 200 ml of acetone gives 6.0 g $[\alpha]_D^{22}$ + 11.1°. Upon two additional recrystallizations of the salt, 1.85 g are obtained, $[\alpha]_D^{22}$ + 13.2°. Further recrystallization of the salt from acetone does not increase the specific rotation. The salt (1.85 g) is dissolved in 50 ml of warm methanol, filtered from any insolubles, and then poured into a stirred mixture of ice and hydrochloric acid. Following filtration and drying, 1.2 g of the acid are obtained which yield upon crystallization from chloroform 1.0 g of (-) 6-chloro-α-methyl-carbazole-2-acetic acid, m.p. 198-201°C; $[\alpha]_D^{22}$ - 53.0°, (C 1.4 CH_3OH).

Example 4

Preparation of (+) 6-chloro-α-methyl-carbazole-2-acetic acid

A solution of 4.3 g of (-) α-methylbenzylamine in 20 ml of acetone is added to a solution of 9.7 g of partially resolved 6-chloro-α-methyl-carbazole-2-acetic acid (recovered from the filtration of a previous resolution of the racemate). After standing at room temperature for 24 hours, the mixture is filtered and the filter cake is washed with cold acetone to yield after drying 7.3 g. Following two additional recrystallizations from acetone, 1.9 g of (+) 6-chloro-α-methyl-carbazole-2-acetic acid (-) α-methylbenzylamine salt, $[\alpha]_D^{22}$ - 13.6° is obtained. Further recrystallizations from acetone do not change the specific rotation. The salt is dissolved in 50 ml of warm acetone and the solution after

filtration is poured into 500 ml of dilute hydrochloric acid. Following filtration and drying, 1.4 g are obtained, which upon crystallization from chloroform give 0.9 g of (+) 6-chloro-α-methyl-carbazole-2-acetic acid, m.p. 198-201°C, $[\alpha]_D^{22}$ + 53.2°, (c 1.33, CH_3OH).

Example 5

Preparation of 6-chloro-α-methylcarbazole-2-acetic acid t-butyl ester

A solution of 2 g of 6-chloro-α-methylcarbazole-2-acetic acid, which can be prepared according to the process of example 2, in 10 ml of tetrahydrofuran is added dropwise to a stirred solution of 1.4 g of 1,1-carbonyl diimidazole in 10 ml of tetrahydrofuran. The stirred reaction mixture is heated to reflux. After the reaction has been stirred at reflux temperature for 1 hour (carbon dioxide is given off by the reaction mixture), it is cooled to 25°C and a solution of 0.5 g of sodium-t-butoxide, 5 g of t-butyl alcohol and 10 ml of tetrahydrofuran is added dropwise over the course of 5 minutes. Following the last addition, the stirred reaction mixture is heated to reflux and maintained there for 4 hours. When the reaction has cooled to room temperature, it it concentrated to dryness under reduced pressure. The residue is partitioned between ether and 2N potassium carbonate. The ether layer is separated, washed by extraction with water and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the ether, 2.2 g are obtained. Crystallization from aqueous ethanol gives 1.7 g

of 6-chloro-α-methylcarbazole-2-acetic acid t-butyl ester, having a m.p. of 152-154°C.

Example 6

Preparation of 9-acetyl-6-chloro-α-methylcarbazole-2-acetic acid

A solution of 4 g of 6-chloro-α-methylcarbazole-2-acetic acid tert. butyl ester, which can be prepared according to the process of example 5, 70 ml of chloroform, 3 ml of acetic anhydride and 1 drop of concentrated sulfuric acid is stirred at reflux temperature for 3 hours. The reaction mixture is concentrated to dryness under reduced pressure, and the residue is partitioned between chloroform and dilute cold potassium bicarbonate. The chloroform layer is separated, washed by extraction with water and dried over magnesium sulfate. Following filtration of the desiccant and evaporation of the ether solution, 1.9 g of the acetylated ester are obtained. The crude product without further purification is stirred and heated between 210-220°C under an atmosphere of dry nitrogen for 30 minutes. Upon cooling to room temperature, the reaction mixture is partitioned between ether and cold dilute potassium bicarbonate. The aqueous portion is separated and the ether is again extracted with cold dilute potassium bicarbonate. Ice is added to the combined potassium bicarbonate extracts and the solution is made slightly acidic with cold 6N hydrochloric acid. The acid that separates is removed by filtration, washed with cold water and air dried; yielding 0.7 g. Following recrystallization from ethyl acetate,

0.5 g of 9-acetyl-6-chloro-α-methylcarbazole-2-acetic acid, having a m.p. of 180-182°C are obtained.

Example 7

Preparation of 6-acetamidocarbazole-2-acetic acid ethyl ester

A mixture of 1.8 g of 6-acetamido-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester, which can be prepared according to the process of example 1E, 0.3 g of 10 percent palladium on carbon black and 30 ml of dry xylene is refluxed and stirred under an atmosphere of dry nitrogen for 48 hours. The mixture is cooled to 70°C, diluted with warm ethanol and filtered through celite. The filter cake is washed several times with warm ethanol. The filtrate and washings are combined and concentrated to dryness under reduced pressure; yielding 1.6 g. Upon crystallization from ethanol, 0.8 g of 6-acetamidocarbazole-2-acetic acid ethyl ester, having a m.p. of 208-210°C are obtained.

Example 8

Preparation of 6-aminocarbazole-2-acetic acid ethyl ester hydrochloride

A solution of 6-acetamidocarbazole-2-acetic acid ethyl ester, which can be prepared according to the process of example 7, and 40 ml of 1N alcoholic hydrogen chloride is refluxed and stirred under an atmosphere of dry nitrogen for 6 hours. The solution is concentrated to dryness under reduced

pressure and the residue is crystallized from a solution of ethyl acetate and ethanol; yielding 0.5 g of 6-aminocarbazole-2-acetic acid ethyl ester hydrochloride, having a m.p. of 231-232°C (dec.).

Example 9

Preparation of racemic 6-chloro-α-methylcarbazole-2-acetic acid methyl ester

A mixture of 1 g of 6-chloro-α-methylcarbazole-2-acetic acid, which can be prepared according to the process of example 1, 100 ml of methanol and 3 drops of concentrated sulfuric acid is stirred thoroughly and allowed to stand at room temperature for 24 hours. The solution is concentrated to dryness under reduced pressure and the residue is partitioned between ether and dilute sodium carbonate. The ether layer is separated and washed by extraction with water and dried over anhydrous sodium sulfate. After filtration of the desiccant and evaporation of the ether, 1.2 g of ester are obtained. Recrystallization from hexane affords 0.7 g of racemic 6-chloro-α-methylcarbazole-2-acetic acid methyl ester, having a m.p. of 111-112°C.

Example 10

Preparation of 6-chloro-α-methylcarbazole-2-acetic acid-2-dimethylamino-ethyl ester

A solution of 3 g of 6-chloro-α-methylcarbazole-2-acetic acid in 10 ml of dimethylformamide is added to a stirred

mixture of 0.48 g of a 54.5 percent dispersion of sodium hydride (in mineral oil) in 30 ml of dimethylformamide. After the addition, the mixture is stirred for 1 hour at room temperature and a solution of freshly liberated dimethylamino-ethylchloride in 10 ml of dimethylformamide is added dropwise over the course of 10 minutes. After the last addition, the reaction mixture is stirred and heated with the temperature maintained at about 70°C for 4 hours. The warm reaction mixture is poured on to 300 g of ice and when the ice melts the mixture is extracted with ether. The ether solution is in turn extracted with dilute potassium carbonate followed by water and the washed ether solution is dried over anhydrous magnesium sulfate. After the desiccant has been removed by filtration and the ether evaporated under reduced pressure, 2.7 g remain. Crystallization of the residue from a solution of ether and hexane gives 2.1 g of 6-chloro-α-methylcarbazole-2-acetic acid-2-dimethylamino-ethyl ester, having a m.p. of 89-90°C.

Example 11

Preparation of 6-chloro-9-ethoxycarbonylmethyl-α-methyl-carbazole-2-acetic acid ethyl ester

A solution of 1.5 g of 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester, prepared according to the process of example 9, in 10 ml of dimethylformamide is slowly added to a stirred mixture of 0.25 g of a 54.5 percent dispersion in mineral oil of sodium hydride in 10 ml of dimethylformamide.

After the addition, the mixture is stirred for 30 minutes at room temperature under an atmosphere of dry nitrogen and a solution of 1 g of ethyl chloroacetate in 5 ml of dimethylformamide is added dropwise over the course of 10 minutes. After the last addition, the reaction mixture is stirred and heated to about 60°C for 7 hours and then poured into 300 ml of ice water. The mixture is extracted with ether. The ether extract is washed by extraction with water and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and evaporation of the ether, 1.6 g remain. Trituration of the residue with a mixture of hexane and ether followed by filtration gives 1.0 g m.p. 80-87°C. Recrystallization from methanol gives 0.7 g of 6-chloro-9-ethoxycarbonylmethyl-α-methylcarbazole-2-acetic acid ethyl ester, having a m.p. of 87-88°C.

Example 12

Preparation of 9-acetyl-6-chloro-α-methylcarbazole-2-acetic acid methyl ester

A solution of 2.0 g of 6-chloro-α-methylcarbazole-2-acetic acid methyl ester, 20 ml of chloroform, 1 ml of acetic anhydride and 1 drop of concentrated sulfuric acid is stirred and heated at reflux temperature. After 3 hours at reflux, the reaction is cooled and concentrated to dryness under reduced pressure. The residue is partitioned between ether and cold dilute sodium bicarbonate. The ether layer is separated, washed by extraction with water and dried over anhydrous magnesium sulfate. Following filtration of the desiccant and

evaporation of the ether, 1.9 g are obtained. Crystallization from a solution of ether and hexane gives 1.1 g of 9-acetyl-6-chloro-α-methylcarbazole-2-acetic acid methyl ester, having a m.p. of 86-87°C.

Example 13

Preparation of 6-dimethylaminocarbazole-2-acetic acid ethyl ester hydrochloride

A mixture of 1.5 g of 6-aminocarbazole-2-acetic acid ethyl ester, which can be prepared according to the process of example 8, 1/2 teaspoon of Raney nickel, 100 ml of methanol and 1.3 g of 30 percent aqueous formaldehyde is shaken in a Parr bomb under an atmosphere of hydrogen (3,8 atm) at room temperature for 4 hours. The catalyst is removed by filtration through celite and the filtrate is concentrated to dryness under reduced pressure. The residue is partitioned between chloroform and dilute sodium bicarbonate. The chloroform layer is separated, washed by extraction with water and dried over anhydrous sodium sulfate. After the desiocant has been removed by filtration, dry hydrogen chloride is added to the filtrate. The salt is filtered and washed with ether. Upon air drying, 0.8 g are obtained. Recrystallization from a mixture of methanol and ethyl acetate gives 0.3 g of 6-dimethylamino-carbazole-2-acetic acid ethyl ester hydrochloride, having a m.p. of 129-131°C.

Example 14

Preparation of 6-hydroxycarbazole-2-acetic acid

A mixture of 1 g of 6-methoxycarbazole-2-acetic acid ethyl ester, 5 ml of glacial acetic acid and 5 ml of 40 percent aqueous hydrobromic acid was stirred at reflux temperature for 5 hours and the warm solution was poured into 800 ml of stirred water. Stirring was continued for 20 minutes. The mixture was filtered, washed with water and air dried; yielding 0.6 g of a tan solid (which gave a slight positive test with ferric chloride). Recrystallization from methanol afforded 0.3 g of 6-hydroxycarbazole-2-acetic acid, having a m.p. of 280-282°C.

Example 15

Preparation of rac. 6-chloro-α-methyl-carbazole-2-acetic acid ethyl ester

A mixture of 10 g of 6-chloro-α-methyl-carbazole-2-acetic acid and 400 ml of ethanol containing 2 g hydrogen chloride (gas) is refluxed and stirred under an atmosphere of nitrogen for 12 hours and allowed to remain at room temperature overnight. Benzene (50 ml) is added and the reaction mixture is concentrated to dryness under reduced pressure. The residue is dissolved in 200 ml of ethanol (2B). Thereafter, 2 g of hydrogen chloride (gas) are added and the solution is again refluxed for 5 hours. The reaction mixture is cooled (about 50°C). Then, 50 ml of benzene are added and the solution is concentrated to dryness. The residue is dissolved

in ether (400 ml). The ether solution is extracted with dilute potassium carbonate (100 ml of 0.01 M) and then with water (2 x 100 ml). Following drying over anhydrous magnesium sulfate, the desiccant is removed by filtration and the ether evaporated; yielding 10.6 g (96%). Recrystallization from methanol yields 8.1 g of rac. 6-chloro-α-methyl-carbazole-2-acetic acid ethyl ester (74%) having m.p. of 106-107°C.

Example 16

Preparation of 2-(6-chloro-2-carbazolyl)propanol

Into a 500 ml, 3-neck flask equipped with a stirrer, condenser, thermometer, dropping funnel and under an atmosphere of dry nitrogen are placed 30 ml of ether and 0.5 g of lithium aluminum hydride. The mixture is stirred and a solution of 1 g of 6-chloro-α-methyl-carbazole-2-acetic acid ethyl ester in 80 ml of ether is added dropwise over the course of 20 minutes. After the addition is completed, the reaction mixture is heated (water bath) to reflux and allowed to reflux and stirred for 10 hours. Then, the reaction mixture is cooled by means of an ice water bath and 30 ml of cold water are added dropwise at such a rate that the temperature never exceeds +10°C. Following the addition of water, the mixture is stirred for 1.5 hours at room temperature and filtered. The filter cake and the flask are washed with two 25 ml portions of ether. The combined filtrates and washings are dried over anhydrous magnesium sulfate. Filtration of the desiccant and evaporation of the ether give a residue of 0.8 g (93.3%). Recrystallization of the product

from benzene gives 0.7 g (81.5%) of 2-(6-chloro-2-carbazolyl) propanol having m.p. of 170-171.5°C.

Example 17

In accordance with the procedure of Example 15, (-) 6-chloro-α-methylcarbazole-2-acetic acid is converted to the corresponding optically active 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester. Then, in accordance with the procedure of Example 16, the optically active 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester is converted to the (+) 2-(6-chloro-2-carbazolyl)propanol having a m.p. of 186-187.5°C (benzene) $[\alpha]_D^{22}$ = +20.6 (c 1.81 CH_3OH).

Example 18

In accordance with the procedure of Example 15, (+) 6-chloro-α-methylcarbazole-2-acetic acid is converted to the corresponding optically active 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester. Then, in accordance with the procedure of Example 16, the optically active 6-chloro-α-methylcarbazole-2-acetic acid ethyl ester is converted to the (-) 2-(6-chloro-2-carbazolyl)propanol having a m.p. of 186-186.5°C, $[\alpha]_D^{22}$ = -20.6 (c 1.6 CH_3OH).

Example 19

Suppositories of the following composition are manufactured in conventional manner:

	Per 1.3 g Suppository
6-chloro-α-methyl-carbazole-2-acetic acid	0.025 g
Wecobee M*	1.230 g
Carnauba Wax	0.045 g

* E.F. Drew Company, 522 Fifth Avenue, New York, N.Y.

Example 20

Tablets of the following composition are manufactured in conventional manner:

	Per Tablet
6-chloro-α-methyl-carbazole-2-acetic acid	25.00 mg
Lactose	64.50 mg
Corn Starch	10.00 mg
Magnesium Stearate	0.50 mg

Example 21

Capsules of the following composition are manufactured in conventional manner:

	Per Capsule
6-chloro-α-methyl-carbazole-2-acetic acid	50 mg
Lactose	125 mg
Corn Starch	30 mg
Talc	5 mg
Total Weight	210 mg

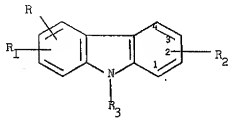
Example 22

Parenteral Formulation

Each 1 cm^3 ampul contains:	Per cm^3:
6-chloro-α-methyl-carbazole-2-acetic acid	10.2 mg (2 percent excess)
Methyl Paraben	1.8 mg
Propyl Paraben	0.2 mg
Sodium Hydroxide, q.s. ph	9.0
Water for Injection, q.s. ad	1 cm^3

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

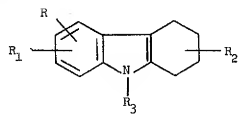
1. Process for the preparation of carbazoles of the general formula



I

wherein R is hydrogen or halogen, R_1 is halogen, hydroxy, cyano, lower alkyl, lower alkoxy, acetamido, lower alkylthio, trifluoromethyl, nitro, amino, mono- or di-lower alkylamino, or di-lower alkyl sulfamoyl; R_2 is

wherein A is hydroxy, or a grouping  , wherein B is hydroxy, lower alkoxy, amino, mono- or di-lower alkylamino, or di-lower alkylamino-lower alkoxy, Y and X are hydrogen or lower alkyl; n is 1 or 2; and R_3 is hydrogen, lower alkyl, lower alkanoyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl or benzyl or R_1 is hydrogen, when R, X and R_3 are hydrogen, Y is lower alkyl and B is hydroxy or lower alkoxy; the term "lower" referring to groups which contain from 1 to 4 carbon atoms, when B is hydroxy salts thereof with bases; and when R_1 is amino or mono- or di-lower alkylamino, and/or when B is di-lower alkylamino-lower alkoxy, addition salts thereof with acids, characterized in that a compound of the formula



II

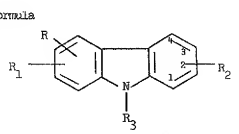
wherein R, R_1, R_2 and R_3 are as above,

is reacted with an aromatizing agent, that in the production of an ester of the

[A]

formula I, wherein B is lower alkoxy, an obtained acid of the formula I, wherein B is hydroxy is esterified, that in the production of an acid of the formula I, wherein R_3 is carboxy-lower alkyl or B is hydroxy, an obtained ester of the formula I, wherein R_3 is lower alkoxycarbonyl-lower alkyl or B is lower alkoxy, is hydrolysed, that if desired, in an obtained compound of the formula I, wherein R_3 is a hydrogen atom, this atom is converted into a lower alkanoyl or lower alkoxycarbonyl-lower alkyl group, that in the production of a compound of the formula I, wherein R_1 is amino, an obtained compound of the formula I, wherein R_1 is acetamido, is reacted with an inorganic acid, that in the production of a compound of the formula I, wherein R_1 is di-lower alkylamino, an obtained compound of the formula I, wherein R_1 is amino, is alkylated, that in the production of a compound of the formula I, wherein R_1 or A is hydroxy, an obtained ether of the formula I, wherein R_1 or A is lower alkoxy, is hydrolysed, that, if desired, in an obtained compound of the formula I, wherein A is a hydroxy group, this group is converted into a lower alkoxy, that in the production of an alcohol of the formula I, wherein A is hydroxy, an obtained ester of the formula I, wherein B is lower alkoxy is reduced, that, if desired, in an obtained acid of the formula I, wherein B is hydroxy, or in a salt thereof with a base, the group B is converted into di-lower alkylamino-lower alkoxy, that in the production of an optically active isomer of a compound of the formula I, an obtained racemate of the formula I is resolved into its optically active isomers and the desired isomer is isolated and that in the production of a salt of a compound of the formula I, wherein B is hydroxy or wherein R_1 is amino or mono- or di-lower alkylamino and/or B is di-lower alkylamino-lower alkoxy, such a compound of the formula I is reacted with a base or an acid.

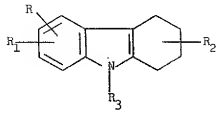
2. Process according to claim 1 for the preparation of carbazoles of the formula



I

wherein R is hydrogen, halogen; R_1 is halogen, hydroxy, cyano, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, nitro, amino, mono- or di-lower alkylamino or di-lower alkylsulfamoyl, R_2 is

wherein A is hydroxy, or a grouping -C - B, wherein B is hydroxy, lower alkoxy, amino, mono- or di-lower alkylamino, or di-lower alkylamino-lower alkoxy; Y and X are hydrogen or lower alkyl; n is 1 or 2; and R_3 is hydrogen, lower alkyl, lower alkanoyl, or benzyl; or R_1 is hydrogen when R, X and R_3 are hydrogen, Y is lower alkyl and B is hydroxy or lower alkoxy;
when B is hydroxy, salts thereof with bases; and when R_1 is amino or mono- or di-lower alkylamino, and/or when B is di-lower alkylamino-lower alkoxy, addition salts thereof with acids, characterized in that a compound of the formula



II

wherein R, R_1, R_2 and R_3 are as above,
is reacted with an aromatizing agent, that in the production of an acid of the formula I, wherein B is hydroxy, an obtained ester of the formula I, wherein B is lower alkoxy, is hydrolysed, that in the production of an alcohol of the formula I, wherein A is hydroxy, an obtained ether of the formula I, wherein A is lower alkoxy, is hydrolysed, that if desired in an obtained acid of the formula I, wherein B is hydroxy, or in a salt thereof with a base, the group B is converted into di-lower alkylamino-lower alkoxy, that in the production of an optically active isomer of a compound of the formula I, an obtained racemate of the formula I is resolved into its optically active isomers and the desired isomer is isolated and that in the production of a salt of a compound of the

[A]

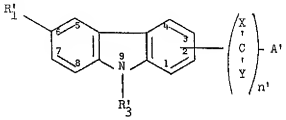
formula I, wherein B is hydroxy, or wherein R_1 is amino or mono- or di-lower alkylamino, and/or B is di-lower alkylamino-lower alkoxy, such a compound of the formula I is reacted with a base or an acid.

3. Process according to claim 1 for the preparation of a compound of the formula I, wherein A or B is hydroxy, characterized in that a compound of the formula II wherein A or B is hydroxy, is utilized as starting material.

4. Process according to claim 1 for the preparation of a compound of the formula I, wherein R is hydrogen, characterized in that a compound of the formula II, wherein R is hydrogen is utilized as starting material.

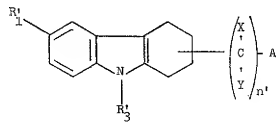
5. Process according to claim 1 for the preparation of a compound of the formula I, wherein R_1 is halogen, characterized in that a compound of the formula II, wherein R_1 is halogen is utilized as starting material.

6. Process according to claim 1 for the preparation of a compound of the formula



I'

wherein n' is 1 and A' is carboxy or n' is 2 and A' is hydroxy; R'_1 is halogen, lower alkyl or lower alkoxy; R'_3 is hydrogen or lower alkyl,
and salts of the compounds of formula I', wherein A' is carboxy, with bases, characterized in that a compound of the formula



II'

wherein n', R'_1, R'_3 and A' are as above,

is utilized as starting material.

7. Process according to claim 1 for the preparation of racemic 6-chloro-α-methyl-carbazole-2-acetic acid, characterized in that 6-chloro-α-methyl-1,2,-3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is utilized as starting material of the formula II.

8. Process according to claim 1 for the preparation of (+) 6-chloro-α-methyl-carbazole-2-acetic acid, characterized in that 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is utilized as starting material of the formula II.

9. Process according to claim 1 for the preparation of (-) 6-chloro-α-methyl-carbazole-2-acetic acid, characterized in that 6-chloro-α-methyl-1,2,3,4-tetrahydrocarbazole-2-acetic acid ethyl ester is utilized as starting material of the formula II.

10. Process according to claim 1 for the preparation of 6-chloro-carbazole-2-acetic acid, characterized in that 6-chloro-1,2,3,4-tetrahydro-carbazole-2-acetic acid ethyl ester is utilized as starting material of the formula II.

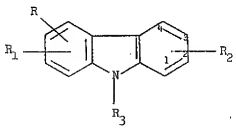
11. Process according to claim 1 for the preparation of 2-(6-chloro-2-carbazolyl)propanol, characterized in that 6-chloro-α-methyl-1,2,3,4-tetrahydro-carbazole-2-acetic acid ethyl ester is utilized as starting material of the formula II.

12. Process according to claim 1 for the preparation of (+) 2-(6-chloro-2-carbazolyl)propanol, characterized in that 6-chloro-α-methyl-1,2,3,4-tetra-hydrocarbazole-2-acetic acid ethyl ester is utilized as starting material of the formula II.

13. Process according to claim 1 for the preparation of (-) 2-(6-chloro-2-carbazolyl)propanol, characterized in that 6-chloro-α-methyl-1,2,3,4-tetra-hydrocarbazole-2-acetic acid ethyl ester is utilized as starting material of the formula II.

14. Process according to claim 1 for the preparation of 6-chloro-9-methyl-carbazole-1-acetic acid characterized in that 6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole-1-acetic acid ethyl ester is utilized as starting material of the formula II.

15. Carbazoles of the general formula



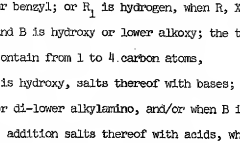
I

wherein R is hydrogen or halogen; R_1 is halogen, hydroxy, cyano, lower alkyl, lower alkoxy, acetamido, lower alkylthio, trifluoromethyl, nitro, amino, mono- or di-lower alkylamino, or di-lower alkylsulfamoyl; R_2 is

wherein A is hydroxy, or a grouping $-C-B$, wherein B is hydroxy, lower alkoxy, amino, mono- or di-lower alkylamino, or di-lower alkylamino-lower alkoxy, Y and X are hydrogen or lower alkyl; n is 1 or 2; and R_3 is hydrogen, lower alkyl, lower alkanoyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl or benzyl; or R_1 is hydrogen, when R, X and R_3 are hydrogen, Y is lower alkyl and B is hydroxy or lower alkoxy; the term "lower" referring to groups which contain from 1 to 4 carbon atoms,

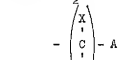
when B is hydroxy, salts thereof with bases; and when R or R_1 is amino or mono- or di-lower alkylamino, and/or when B is di-lower alkylamino-lower alkoxy, addition salts thereof with acids, whenever prepared by the process as claimed in claim 1, or by an obvious chemical equivalent thereof.

16. Carbazoles according to claim 15 of the formula



I

wherein R is hydrogen, halogen; R_1 is halogen, hydroxy, cyano, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, nitro, amino, mono- or di-lower alkylamino, or di-lower alkylsulfamoyl, R_2 is



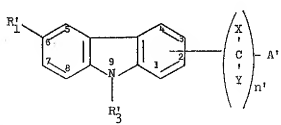
wherein A is hydroxy, or a grouping $-\overset{O}{\overset{\|}{C}}-B$, wherein B is hydroxy, lower alkoxy, amino, mono- or di-lower alkylamino, or di-lower alkylamino-lower alkoxy; Y and X are hydrogen or lower alkyl; n is 1 or 2; and R_3 is hydrogen, lower alkyl, lower alkanoyl, or benzyl or R_1 is hydrogen, when R, X and R_3 are hydrogen, Y is lower alkyl and B is hydroxy or lower alkoxy;
when B is hydroxy salts thereof with bases, and when R_1 is amino or mono- or di-lower alkylamino, and/or when B is di-lower alkylamino-lower alkoxy, addition salts thereof with acids, whenever prepared by the process as claimed in claim 2 or by an obvious chemical equivalent thereof.

17. Carbazoles according to claim 15 of the formula I, wherein A or B is hydroxy, whenever prepared by the process as claimed in claim 3 or by an obvious chemical equivalent thereof.

18. Carbazoles according to claim 15 of the formula I, wherein R is hydrogen, whenever prepared by the process as claimed in claim 4 or by an obvious chemical equivalent thereof.

19. Carbazoles according to claim 15 of the formula I, wherein R_1 is halogen, whenever prepared by the process as claimed in claim 5 or by an obvious chemical equivalent thereof.

20. Carbazoles according to claim 15 of the formula



I'

wherein n' is 1 and A' is carboxy or n' is 2 and A' is hydroxy; R'_1 is halogen,

lower alkyl or lower alkoxy; R_1 is hydrogen or lower alkyl, and salts of the compounds of the formula I' wherein A' is carboxy, whenever prepared by the process as claimed in claim 6 or by an obvious chemical equivalent thereof.

21. Carbazole according to claim 15, i.e. racemic 6-chloro-α-methyl-carbazole-2-acetic acid, whenever prepared by the process as claimed in claim 7 or by an obvious chemical equivalent thereof.

22. Carbazole according to claim 15 i.e. (+) 6-chloro-α-methyl-carbazole-2-acetic acid, whenever prepared by the process as claimed in claim 8, or by an obvious chemical equivalent thereof.

23. Carbazole according to claim 15, i.e. (-) 6-chloro-α-methyl-carbazole-2-acetic acid, whenever prepared by the process as claimed in claim 9 or by an obvious chemical equivalent thereof.

24. Carbazole according to claim 15, i.e. 6-chloro-carbazole-2-acetic acid, whenever prepared by the process as claimed in claim 10 or by an obvious chemical equivalent thereof.

25. Carbazole according to claim 15, i.e. 2-(6-chloro-2-carbazolyl)-propanol, whenever prepared by the process as claimed in claim 11, or by an obvious chemical equivalent thereof.

26. Carbazole according to claim 15 i.e. (+) 2-(6-chloro-2-carbazolyl)-propanol, whenever prepared by the process as claimed in claim 12 or by an obvious chemical equivalent thereof.

27. Carbazole according to claim 15 i.e. (-) 2-(6-chloro-2-carbazolyl)-propanol, whenever prepared by the process as claimed in claim 13 or by an obvious chemical equivalent thereof.

28. Carbazole according to claim 15 i.e. 6-chloro-9-methyl-carbazole-1-acetic acid, whenever prepared by the process as claimed in claim 14 or by an obvious chemical equivalent thereof.

A